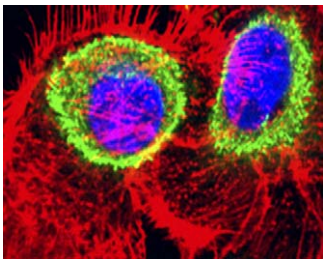
In This Issue

Cell



Deubiquitination Keeps Oncogene in Check

PAGE 665

Mutations in CYLD, a deubiquitinating enzyme, cause tumors that originate from hair follicle keratinocytes. Massoumi et al. show that the wild-type CYLD prevents the formation of tumors by deubiquitinating the oncogene Bcl-3, thereby denying it access to the nucleus. In mice lacking CYLD, Bcl-3 accumulates in the nucleus and stimulates proliferation by binding to members of the NF-κB family of transcription factors. This study is the first demonstration of a specific mechanism by which Bcl-3 is kept in check.

Structure of a Histone Demethylase

PAGE 691

Histone demethylases remove methyl groups from the lysine residues of histone tails and thereby contribute to transcriptional regulation of target genes. The JmjC-containing protein JMJD2A has been characterized as a site-specific histone tri-methyl demethylase. Here, Chen et al. report the crystal structure of the core catalytic domain of JMJD2A, defining unique elements that form a potential substrate binding pocket. The structure, combined with additional biochemical experiments, provides insight into the molecular mechanism of substrate selection by the JMJD2 histone demethylase family.

FACT-Check on Transcription Elongation

PAGE 703

RNA polymerase II must overcome the nucleosomal barriers present in chromatin to synthesize RNA. Pavri et al. designed a fully reconstituted chromatin and transcription system to define the minimal factors required for transcription elongation. In conjunction with the histone chaperone FACT, monoubiquitination of histone H2B at lysine 120 is required for robust and efficient transcription elongation. This histone modification impacts on the extent of transcript elongation in a FACT-dependent manner facilitating RNA polymerase migration along the transcription unit. These studies identify the functional relevance of one of the several histone modifications that positively regulate transcription.

A Key to the Mitotic Exit Door

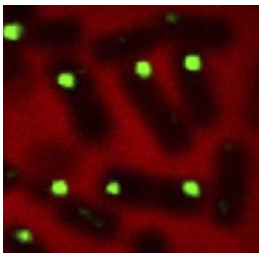
PAGE 719

Following chromosome segregation, cells have to exit mitosis and undergo cytokinesis before entering G1 of the next cell cycle. Although we have a relatively good grasp of the regulation of mitotic entry—driven by upregulation of mitotic kinases—the control of mitotic exit is still much less understood. In budding yeast, Queralt et al. show that the protease that separates sister chromatids, separase, interacts with and downregulates $PP2A^{Cdc55}$ phosphatase. Downregulation of PP2A allows mitotic kinases to activate their own key antagonist, the phosphatase Cdc14. Thus, separase provides an early impetus to inhibit mitotic kinase activity, a key event required for mitotic exit.

Homing in on DNA Damage in Prokaryotes

PAGE 679

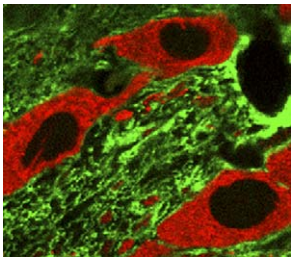
The elaborate DNA repair machinery of eukaryotic cells has been studied intensively, but the machinery in prokaryotes is less well understood. Bejerano-Sagie et al. now show that the DisA protein expressed during an early stage of sporulation in the bacterium *Bacillus subtilis* acts as a DNA-damage checkpoint protein. DisA molecules are organized into a single focal assembly that moves dynamically within the bacterial cell searching for DNA lesions. When damage is encountered, the DisA assembly pauses at the lesion site. The stalled complex delays sporulation, enabling the damage to be repaired. This study provides new insights into how proteins proofread DNA in prokaryotic cells and activate a developmental checkpoint response.



Picky PI3 Kinase Inhibitors

PAGE 733

Phosphoinositide 3-kinases (PI3-Ks) have been implicated in diverse physiological processes including cell growth and intracellular trafficking, but the unique roles of the various PI3-K isoforms are unclear. Knight et al. describe a panel of isoform-specific PI3-K inhibitors and reveal the structural basis for their selectivity by solving the crystal structures of three inhibitors bound to the PI3-K isoform p110gamma. Using the inhibitors, the authors find that the isoform p110alpha is required for insulin signaling. These experiments illustrate how selective pharmacology can be used to dissect the function of different kinase isoforms and provide new insights into the regulation of insulin signaling.



Astrocytic Serine Assists Synapses

PAGE 775

A central player in excitatory synaptic transmission is the NMDA receptor, which requires both glutamate and a coagonist, such as D-serine, for activity. Panatier et al. now show that astrocytes, a type of glial cell, control NMDA receptor activity in neurons through the synthesis and release of D-serine. The authors examine the activity of rat hypothalamic neurons, whose coverage by astrocytes changes during lactation. They show that the degree of astrocytic coverage determines NMDA receptor and synaptic activity. These results establish the active contribution of astrocytes to synaptic transmission in the brain.

PAMP Receptor Transfers Immunity

PAGE 749

Innate immunity in higher eukaryotes involves the recognition of pathogen-associated molecular patterns (PAMPs) by specific receptors. Zipfel et al. now identify the *Arabidopsis* PAMP receptor for an elongation factor (EF-Tu) from *Agrobacterium tumefaciens*, a bacterium that infects many crops, causing tumor-like growths. The authors find that *Arabidopsis* mutants lacking this receptor are more susceptible to *Agrobacterium* infection, while expression of the receptor in tobacco plants, which normally lack the receptor, allows them to mount an immune response. The findings thus suggest an approach for making crops more resistant to *Agrobacterium* infection.

Classic Coactivator Steps out of the Nucleus

PAGE 761

OCA-B, a cell type-specific transcriptional coactivator, is critical for antigen-dependent immune responses in B cells. Now Siegel et al. show that OCA-B not only regulates expression of its transcriptional targets within the nucleus, but also functions in signaling pathways involving the SYK kinase, which has critical roles in both pre-B and B cell signaling. OCA-B binds to SYK and regulates its stability in the cytoplasm of pre-B cells. These findings indicate a new and unexpected function of a classic coactivator in B cell development.

The Mighty "Minis'"

PAGE 785

When neuronal action potentials are blocked, synaptic strength slowly increases to compensate. Now, Sutton et al. show that miniature synaptic transmissions or "minis," which release neurotransmitter independent of action potentials, shape this compensatory response. When both "minis" and action potentials are blocked, the compensatory upregulation of synaptic strength is accelerated due to an increase in protein synthesis in postsynaptic dendrites. Thus, these results indicate that "minis" stabilize synaptic function by suppressing local protein synthesis in dendrites.

Attacking the Ataxia Protein Network

PAGE 801

Several inherited cerebellar ataxias share clinical and pathological features, most notably, loss of balance and Purkinje cell degeneration. Over 20 ataxia-causing genes have been identified, but whether the corresponding proteins are functionally related was not known. Lim and colleagues developed a protein-protein interaction network for 23 ataxia-causing proteins. Surprisingly, they found that the majority (18/23) of the ataxia proteins interact, and that several genetic modifiers of the phenotypes are also physical interactors of the ataxia proteins. This study reveals that the protein interaction network for ataxia is highly interconnected and provides a novel approach to study complex disorders.